(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 134 218 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
19.09.2001 Bulletin 2001/38

(51) Int Cl.7: **C07D 311/72**

(21) Application number: **01105979.7**

(22) Date of filing: **10.03.2001**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **17.03.2000 EP 00105672**

(71) Applicant: **F. HOFFMANN-LA ROCHE AG**
4070 Basel (CH)

(72) Inventors:
- **Bonrath, Werner**
  79115 Freiburg (DE)
- **Haas, Alois**
  44797 Bochum (DE)
- **Hoppmann, Eike**
  44801 Bochum (DE)
- **Netscher, Thomas**
  79189 Bad Krozingen (DE)
- **Pauling, Horst**
  4147 Aesch (CH)

(54) Process for manufacturing (all-rac.)-alpha-Tocopherol

(57) A process for the manufacture of (all-rac.)-α-tocopherol by the acid-catalyzed condensation of trimethylhydroquinone with isophytol or phytol is characterized by carrying out the condensation in the presence of a tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methane or a metal salt thereof as the catalyst in an organic solvent. In addition to said metal salt a Bronsted acid, e.g. sulphuric acid, phosphoric acid or p-toluenesulphonic acid, may be used as a co-catalyst. The product of the process is the most active member of the vitamin E group.

EP 1 134 218 A1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] The present invention is concerned with a novel process for the manufacture of (all-rac.)-α-tocopherol by the acid-catalyzed condensation of trimethylhydroquinone (TMHQ) with isophytol (IP) or phytol (PH) in a solvent. As is known, (all-rac.)-α-tocopherol (or as it has mostly been denoted in the prior art, "d,l-α-tocopherol") is a diastereoisomeric mixture of 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyl-tridecyl)-6-chromanol (α-tocopherol), which is the most active and industrially most important member of the vitamin E group.

[0002] Many processes for the manufacture of "d,l-α-tocopherol" (referred to as such in the literature reviewed hereinafter) by the condensation of TMHQ with IP or PH in the presence of a catalyst or catalyst system and in a solvent or solvent system are described in the literature. These processes go back to the work of Karrer et al., Bergel et al. as well as Smith et al. [see Helv. Chim. Acta 21, 520 et seq. (1938), Nature 142, 36 et seq. (1938) and, respectively, Science 88, 37 et seq. (1938) and J. Am. Chem. Soc. 61, 2615 et seq. (1939)]. While Karrer et al. carried out the synthesis of d,l-α-tocopherol from TMHQ and phytyl bromide in the presence of anhydrous zinc chloride ($ZnCl_2$; a Lewis acid), not only Bergel et al. but also Smith et al. used TMHQ and PH as starting materials. In the following years mainly modifications, e.g. alternative solvents and Lewis acids, were developed. From the work of Karrer et al. there was developed in the year 1941 a technically interesting process for the manufacture of d,l-α-tocopherol which was based on the condensation of TMHQ with IP in the presence of the catalyst system $ZnCl_2$/hydrochloric acid (HCl) (US Patent 2 411 969). Later publications, e.g. Japanese Patent Publications (Kokai) 54380/1985, 64977/1985 and 226979/1987 [Chemical Abstracts (C.A.) 103, 123731s (1985), C.A. 103, 104799d (1985) and, respectively, C.A. 110, 39217r (1989)], describe this condensation in the presence of zinc and/or $ZnCl_2$ and a Bronsted (protonic) acid, such as a hydrohalic acid, e.g. HCl, trichloroacetic acid, acetic acid and the like, especially $ZnCl_2$/HCl, as the catalyst system. Disadvantages of these and further published processes featuring $ZnCl_2$ in combination with a Bronsted acid are the corrosive properties of the acids and the contamination of the waste water with zinc ions as a result of the large amount of $ZnCl_2$ required for the catalysis.

[0003] The manufacture of d,l-α-tocopherol by the reaction of TMHQ with phytyl chloride, PH or IP in the presence of boron trifluoride (BF_3) or its etherate (BF_3Et_2O) is described in German Patents 960720 and 1015446 as well as in US Patent 3 444 213. However BF_3 too has corrosive properties.

[0004] Also, the condensation of TMHQ with IP or PH in the presence of a Lewis acid, e.g. $ZnCl_2$, BF_3 or aluminium trichloride ($AlCl_3$), a strong acid, e.g. HCl, and an amine salt as the catalyst system is described in European Patent Publication (EP) 100471. In an earlier patent publication, DOS 2606830, the IP or PH is pretreated with ammonia or an amine before the condensation with TMHQ in the presence of $ZnCl_2$ and an acid is effected. In both cases corrosion problems occur.

[0005] A further interesting method for the manufacture of d,l-α-tocopherol from TMHQ and IP comprises using an isolated TMHQ-BF_3 or -$AlCl_3$ complex and a solvent mixture featuring a nitro compound (DOS 1909164). This process avoids to a large extent the formation of un-desired by-products because it involves mild reaction conditions. The yield of d,l-α-tocopherol, based on IP and the use of the solvent mixture methylene chloride/nitro-methane, is given as 77%. However, the use of such a solvent mixture is disadvantageous.

[0006] The manufacture of d,l-α-tocopherol by the condensation of TMHQ with IP using cation exchange resin complexes of metal ions (Zn^{2+}, Sn^{2+} and Sn^{4+}) is disclosed in Bull. Chem. Soc. Japan 50, 2477-2478 (1977); amongst other disadvantages it gives the product in unsatisfactory yields.

[0007] The use of macroreticular ion exchangers, e.g. Amberlyst® 15, as the catalyst for the condensation of TMHQ with IP is described in US Patent 3459773. However, the d,l-α-tocopherol could not be obtained in the requisite purity.

[0008] EP 603695 describes the manufacture of d,l-α-tocopherol in liquid or supercritical carbon dioxide by the condensation of TMHQ with IP or PH in the presence of acidic catalysts, such as $ZnCl_2$/HCl and ion exchangers. The reported yields are unsatisfactory.

[0009] The condensation in the presence of a catalyst system which consists of iron(II) chloride, metallic iron and HCl gas or aqueous solution is described in DOS 2160103 and US Patent 3789086. The formation of less by-products is advant-ageous compared with the aforementioned process using $ZnCl_2$/HCl. However, corrosion problems and chloride contamination are equally disadvantageous.

[0010] An interesting alternative for the condensation of TMHQ with IP to d,l-α-tocopherol comprises using trifluoroacetic acid or its anhydride as the catalyst (EP 12824). Although in this process the avoidance of HCl is achieved, the catalyst is relatively expensive.

[0011] The use of the heteropoly acid 12-tungstophosphoric or 12-tungstosilicic acid as the catalyst for the condensation of TMHQ with IP was described for the first time in React. Kinet. Catal. Lett. 47(1), 59-64 (1992). d,l-α-Tocopherol could be obtained, using various solvents, in about 90% yield.

[0012] A further process described in the literature [EP 658552; Bull. Chem. Soc. Japan 68, 3569-3571 (1995)] for the synthesis of d,l-α-tocopherol is based on the use of a scandium, yttrium or lanthanide fluorosulphonate, nitrate or sulphate, e.g. scandium trifluoromethanesulphonate, as the catalyst for the condensation. With up to about 10% excess

of IP this process gives yields up to 98%.

[0013] The use of ion-exchanged bentonite, montmorillonite or saponite through treatment with e.g. scandium chloride and other metal salts (yttrium, lanthanum, etc.) as the catalyst for the condensation of TMHQ with IP or PH has as a disadvantage the need for a large amount of catalyst [EP 677520; Bull. Chem. Soc. Japan 69, 137-139 (1996)].

[0014] According to the Examples of EP 694 541 the condensation of TMHQ with IP to α-tocopherol can be achieved in high yields and with a high product purity when such solvents as carbonate esters, fatty acid esters and certain mixed solvent systems are employed, the exemplified catalysis being effected by $ZnCl_2$/HCl. Disadvantages in this process are, in addition to the contamination of the waste water by zinc ions, the usual large "catalyst amount" of $ZnCl_2$ used.

[0015] According to WO 97/28151 the acid-catalysed condensation of TMHQ with IP can be performed in a cyclic carbonate or α-lactone as the solvent. The preferred catalyst is a mixture of orthoboric acid and oxalic, tartaric or citric acid, or boron trifluoride etherate.

[0016] WO 98/21197 describes the manufacture of d,l-α-tocopherol from TMHQ and IP using bis(trifluoromethylsulphonyl)amine or a metal salt thereof optionally together with a strong Bronsted acid, as catalyst in such types of aprotic solvents as aliphatic and cyclic ketones or esters, and aromatic hydrocarbons.

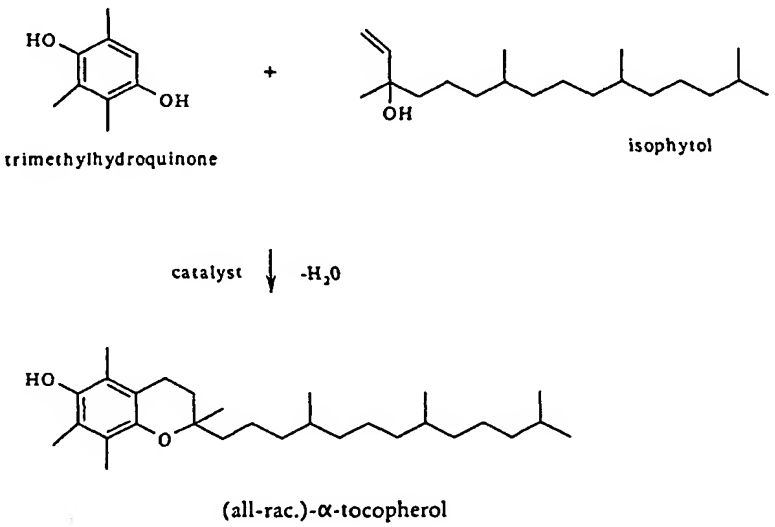
[0017] From the forgoing review it is evident that most of the previously known processes have considerable disadvantages. Thus, corrosion problems occur in all processes in which such acid catalysts as boron trifluoride are used. Toxicity problems with the boron trifluoride adducts also occur, and when iron or zinc is used there is a contamination of the waste water with the metal ions which is today no longer acceptable. In some processes the formation of undesired by-products, e.g. phytyltoluene and chlorophytols, is an especially serious problem.

[0018] The object of the present invention is to provide a process for the manufacture of (all-rac.)-α-tocopherol by the condensation of trimethylhydroquinone with isophytol or phytol in the presence of a catalyst and in a solvent which does not have the disadvantages of previously known procedures. In this respect, it is necessary that the catalyst used has no, or at least a much reduced, corrosive action, is non-toxic, does not contaminate the environment and catalyzes the desired reaction as selectively as possible and in high yields. Furthermore, the catalyst should display its activity in small, really catalytic, amounts and should be readily separable and re-usable several times.

[0019] This object of the present invention is achieved by carrying out the condensation of trimethylhydroquinone with isophytol or phytol in the presence of a so-called CH-acidic compound or a metal salt thereof, which is more particularly a tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methane or a metal tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methide, in an organic solvent.

[0020] The condensation itself is represented in the following Reaction Scheme, showing the reaction with IP only.

Reaction Scheme



trimethylhydroquinone

isophytol

(all-rac.)-α-tocopherol

[0021] Accordingly, the process in accordance with the invention for the manufacture of (all-rac.)-α-tocopherol by

the catalyzed condensation of trimethylhydroquinone with isophytol or phytol, is characterized by carrying out the condensation in the presence of a tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methane or a metal tris (perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methide, of the general formula

$$[(R^1SO_2)_3C]_xR^2 \quad I$$

wherein

R^1 signifies a perfluoroalkyl group C_nF_{2n+1} or pentafluorophenyl,

R^2 signifies a proton or a metal cation selected from the group consisting of boron, magnesium, aluminium, silicon, scandium, titanium, vanadium, vanadyl, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, rhodium, palladium, silver, tin, lanthanum, cerium, praseodymium, neodymium, europium, dysprosium, ytterbium, hafnium, platinum and gold, each in the cationic form,

n signifies an integer from 1 to 10 and

x signifies the corresponding valency of the proton (1) or metal cation (1,2,3 or 4), as the catalyst in an organic solvent.

[0022] Some of the CH-acidic compounds and their metal salts of formula I are known compounds. Thus in Inorg. Chem. 27, 2135- 2137 (1988) K. Seppelt and L. Turowsky describe for the first time the preparation of tris(trifluoromethanesulphonyl)methane, $(CF_3SO_2)_3CH$, and of four salts thereof, viz the potassium, rubidium, silver and cesium salts. The lithium and further metal salts of $(CF_3SO_2)_3CH$ and other tris(perfluoroalkanesulphonyl)methides and their preparation are described in US Patent 5 273 840. Also developing the original work of Seppelt and Turowsky, F.J. Waller et al. describe in J. Org. Chem. 64, 2910 - 2913 (1999) the further preparation of $(CF_3SO_2)_3CH$ and its cesium salt, and also the preparation of the corresponding scandium and ytterbium salts. In Synlett 1999, No. 12, 1990 - 1992, J. Nishikido et al. describe the preparation of scandium, yttrium and, in general, lanthanide (III) tris(perfluorobutanesulphonyl)methide complexes. Further literature concerning the preparation of these and further metal tris(perfluoroalkanesulphonyl)methides includes US Patent 5 554 664 and the many references mentioned in this and in other aforementioned publications.

[0023] The tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methanes or metal salts thereof embraced by the formula I hereinbefore and used as the catalysts in the process of the present invention can be produced according to such published methods or, in the case of those methanes or metal salts thereof which may still not be known, according to analogous methods.

[0024] In the case of the metal tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methides (the metal salts) this catalyst can be used together with a strong Bronsted acid as a co-catalyst in the process of the present invention. The Bronsted acid present in such a catalyst system can be an inorganic or organic acid, examples of which are sulphuric acid, phosphoric acid and p-toluenesulphonic acid. In the case of using a lithium salt as the catalyst of formula I (R^2 being the lithium cation), the use of a Bronsted acid as a co-catalyst is particularly preferred.

[0025] Solvents which can be used in the scope of the present invention are polar or non-polar organic solvents. Suitable classes of polar solvents include aliphatic and cyclic ketones, e.g. isobutyl methyl ketone and diethyl ketone and, respectively, cyclopentanone and isophorone; and aliphatic and cyclic esters, e.g. ethyl acetate and isopropyl acetate, and, respectively, γ-butyrolactone, ethylene carbonate and propylene carbonate. As suitable classes of non-polar solvents there may be mentioned aliphatic hydrocarbons, e.g. hexane, heptane and octane, and aromatic hydrocarbons, e.g. benzene, toluene and the xylenes. The condensation can be effected in a single solvent phase, e.g. in toluene alone as the solvent, or in a biphasic solvent system, e.g. in ethylene carbonate and hexane.

[0026] The process is conveniently effected at temperatures from about 60°C to about 150°C, preferably from about 100°C to about 120°C.

[0027] Furthermore, the molar ratio of trimethylhydroquinone to isophytol/phytol present in the reaction mixture conveniently extends from about 1.3:1 to about 2.5:1, preferably from about 1.5:1 to about 2.2:1, and is most preferably about 2:1.

[0028] The amount of catalyst of formula I used is such that the molar ratio of catalyst to the educt (trimethylhydroquinone or isophytol/phytol) which is in the lesser molar amount (generally the isophytol or phytol) is conveniently about 0.1:100 to about 2:100, i.e. is from about 0.1 mole % to about 2 mole %.

[0029] Conveniently about 10 - 100 ml, preferably about 30 - 60 ml, of organic solvent are used per 10 mmol of

isophytol or phytol, whichever is employed.

[0030] If the process reaction is carried out in in a biphasic solvent system, especially one consisting of a polar solvent, e.g. a cyclic carbonate such as ethylene or propylene carbonate, and a non-polar solvent, e.g. an aliphatic hydrocarbon such as hexane, then the volume ratio of the non-polar solvent to the polar solvent is conveniently in the range from about 0.3:1 to about 5:1, preferably from about 1:1 to about 3:2.

[0031] Moreover, the process reaction is conveniently carried out under an inert gas atmosphere, preferably gaseous nitrogen or argon.

[0032] The actual reaction generally lasts for about 0.2 - 20 hours, preferably about 0.5 - 1 hour.

[0033] The process in accordance with the invention can be carried out batchwise or continuously, and in general operationally in a very simple manner, for example by adding isophytol or phytol, as such or in solution, portionwise to a suspension or solution of the trimethylhydroquinone and the catalyst. The rate at which the isophytol or phytol is added is not critical. Conveniently, isophytol/phytol is added continuously over a period 0.5 to 5 hours. After completion of the isophytol/phytol addition and an appropriate subsequent reaction period the working-up is effected by procedures conventionally used in organic chemistry.

[0034] If desired, the obtained (all-rac.)-α-tocopherol can be converted into its acetate, succinate, poly(oxyethylene) succinate, nicotinate and further known application forms by standard procedures [see, for example, the 5th Edition of Ullmann's Encyclopedia of Industrial Chemistry, Vol. A 27, pages 484-485 (VCH Verlagsgesellschaft mbH, D-69451 Weinheim, 1996)].

[0035] The process in accordance with the invention enables the catalyst used to be separated readily and to be reused several times.

[0036] Advantages in the use of the catalyst in the process in accordance with the invention are, in addition to high yields of (all-rac.)-α-tocopherol, the avoidance of corrosion, the avoidance of waste water contamination with heavy metal ions, the high selectivity as well as the enabled ready isolation of the produced (all-rac.)-α-tocopherol from the mixture after reaction.

[0037] The process in accordance with the invention is illustrated by the following Examples:

Example 1

[0038] 5.23 g (33 mmol) of trimethylhydroquione (TMHQ) are suspended/dissolved in 50 ml of toluene, whereafter 6.8 mg of tris(trifluoromethanesulphonyl)methane are added and the mixture is heated to about 100°C. To the heated mixture with stirring there are added portionwise 6 ml (16.5 mmol) of isophytol over a period of about 60 minutes. Subsequently, the reaction mixture is stirred for a further 30 minutes at100 °C, after which the reaction is determined by GC to have been completed.

[0039] To isolate the crude (all rac.)-α-tocopherol formed in the reaction the solvent is evaporated off under reduced pressure.

[0040] In this manner there are obtained 6.52 g (91.7% theoretical yield) of (all-rac.)-α-tocopherol, as analysed by gas chromatography (GC).

[0041] If desired, the crude product can be converted into its acetate by standard procedures.

Example 2

[0042] 7.69g (49.5 mmol) of trimethylhydroquione suspended/dissolved in a two-phase solvent system consisting 50 ml of heptane and 40 ml of ethylene carbonate, whereafter 13.6 mg of tris(trifluoromethanesulphonyl)methane are added and the mixture is heated to about 95°C. To the stirred heated mixture there are added portionwise11.88 ml (33 mmol) of isophytol over a period of about 20 minutes. Subsequently, the reaction mixture is stirred for a futher 30 minutes at 95 °C, after which the reaction is determined by GC to have been completed.

[0043] To isolate the crude (all-rac.)-α-tocopherol formed in the reaction the heptane is evaporated off by concentration under reduced pressure. The remaining ethylene carbonate phase is then cooled to about 80°C and extracted with 50 ml of fresh heptane. After the phase separation the heptane phase containing the product is evaporated under a reduced pressure of 20 mbar (2 kPa) at 40°C. (The separated off ethylene carbonate phase, containing the catalyst can be reused if desired).

[0044] In this manner there are obtained 13.27 g (96.6% theoretical yield) of (all-rac.)-α-tocopherol, as analysed by GC.

[0045] If desired, the crude product can be converted into its acetate by standard procedures.

Example 3

[0046] In an analogous manner to that described in Example 2, using 40 ml of propylene carbonate instead of 40 ml

of ethylene carbonate as the co-solvent, there are obtained 13.27 g (93.4% theoretical yield) of (all-rac.)-α-tocopherol.

Example 4

[0047] 7.69 g (49.5 mmol) of trimethylhydroquinone are dissolved in 40 ml of ethylene carbonate at 90° C. After addition of 50 ml of heptane, 0.52 g (1.0 mmol) of silver tris(trifluoromethanesulphonyl)methide [$(CF_3SO_2)_3CAg$] are also added to the mixture. Over a period of 20 minutes 11.88 ml (33 mmol) of isophytol are then introduced into the mixture at 94° C. After stirring for 30 minutes the mixture is extracted with 50 ml of fresh heptane. (After phase separation the carbonate phase can be reused if desired). The heptane phase is concentrated under a reduced pressure of 20 mbar (2 kPa) at 40°C,and the crude product analyzed by GC. The yield of (all-rac.)-α-tocopherol is 12.79 g (90 % theoretical yield).

Example 5

[0048] 7.69 g (49.5 mmol) of trimethylhydroquinone are dissolved in 40 ml of ethylene carbonate at 90° C. After addition of 50 ml of heptane, 0.17 g (0.33 mmol) silver tris(trifluoromethanesulphonyl)methide is also added to the mixture. Over a period of 20 minutes 11.88 ml (33 mmol) of isophytol are then introduced into the mixture at 94° C. After stirring for 30 minutes the heptane is distilled off, the reaction mixture cooled to 80° C and the ethylene carbonate phase extracted with 50 ml of fresh heptane. (After phase separation the ethylene carbonate phase can be reused if desired). The heptane phase is concentrated under a reduced pressure of 20 mbar (2 kPa) at 40°C and the crude product analyzed by GC. The yield (all-rac.)-α-tocopherol is 12.43 g (87.5 % theoretical yield).

Example 6

[0049] 7.69 g (49.5 mmol) trimethylhydroquinone arre dissolved in 40 ml of ethylene carbonate at 90° C. After addition of 50 ml of heptane, 0.69 g (0.33 mmol) of zirconium tris(trifluoromethanesulphonyl)methide ([$(CF_3SO_2)_3C]_4Zr$) is also added to the mixture. Over a period of 20 minutes 11.88 ml (33 mmol) of isophytol are then introduced into the mixture at 94° C. After stirring for 30 minutes the heptane is distilled off, the reaction mixture cooled to 80° C and the ethylene carbonate phase extracted with 50 ml of fresh heptane. (After phase separation the ethylene carbonate phase can be reused if desired). The heptane phase is concentrated under a reduced pressure of 20 mbar (2 kPa) at 40°C and the crude product analyzed by GC. The yield of (all-rac.)-α-tocopherol is 12.8 g (90.06 % theoretical yield).

Example 7

[0050] 7.69 g (49.5 mmol) trimethylhydroquinone are dissolved in 40 ml of ethylene carbonate at 90° C. After addition of 50 ml of heptane, 0.292 g (0.33 mmol) of copper tris(trifluoromethanesulphonyl)methide ([$(CF_3SO_2)_3C]_2Cu$) is also added to the mixture. Over a period of 20 minutes 11.88 ml (33 mmol) of isophytol are then introduced into the mixture at 94° C. After stirring for 30 minutes the heptane is distilled off, the reaction mixture cooled to 80° C and the ethylene carbonate phase extracted with 50 ml of heptane. (After phase separation the ethylene carbonate phase can be reused if desired). The heptane phase is concentrated under a reduced pressure of 20 mbar (2 kPa) at 40°C and the crude product analyzed by GC. The yield of (all-rac.)-α-tocopherol is 13.33 g (93.80 % theoretical yield).

Example 8

[0051] 4.4 g (28.3 mmol) trimethylhydroquinone are dissolved in 23 ml of ethylene carbonate at 90° C. After addition of 30 ml of heptane, 0.16 g (0.18 mmol) of vanadyl tris(trifluoromethanesulphonyl)methide ([$(CF_3SO_2)_3C]_2VO$) are added. Over a period of 20 minutes 6.8 ml (18.9 mmol) of isophytol are then introduced into the mixture at 94° C. After stirring for 30 minutes the heptane is distilled off, the reaction mixture cooled to 80° C and the carbonate phase extracted with 30 ml heptane. (After phase separation the ethylene carbonate phase can be reused if desired). The heptane phase is concentrated under a reduced pressure of 20 mbar (2 kPa) at 40°C and the crude product analyzed by GC. The yield of (all-rac.)-α-tocopherol is 7.46 g (91.7% theoretical yield).

Example 9

[0052] 7.69 g (49.5 mmol) trimethylhydroquinone are dissolved in 40 ml ethylene carbonate at 90° C. After addition of 50 ml heptane, 0.582 g (0.33 mmol) of tin tris(trifluoromethanesulphonyl)methide ([$(CF_3SO_2)_3C]_4Sn$) are added. Over a period of 20 minutes 11.88 ml (33 mmol) of isophytol are then introduced into the mixture at 94°C. After stirring for 30 minutes the heptane is distilled off, the reaction mixture cooled to 80° C and the carbonate phase extracted with

30 ml of heptane. (After phase separation the ethylene carbonate phase can be reused if desired). The heptane phase is concentrated under a reduced pressure of 20 mbar (2 kPa) at 40°C and the crude product analyzed by GC. The yield of (all-rac.)-a-tocopherol is 12.74 g (89.67 % theoretical yield).

Claims

1. A process for the manufacture of (all-rac.)-α-tocopherol by the acid-catalyzed condensation of trimethylhydroquinone with isophytol or phytol, which process is **characterized by** carrying out the condensation in the presence of a tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methane or a metal tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methide, of the general formula

$$[(R^1SO_2)_3C]_x\ R^2$$

wherein

R^1 signifies a perfluoroalkyl group, C_nF_{2n+1}, or pentafluorophenyl,

R^2 signifies a proton or a metal cation selected from the group consisting of boron, magnesium, aluminium, silicon, scandium, titanium, vanadium, vanadyl, manganese, iron, cobalt, nickel, copper, zinc, yttrium, zirconium, rhodium, palladium, silver, tin, lanthanum, cerium, praseodymium, neodymium, europium, dysprosium, ytterbium, hafnium, platinum and gold, each in the cationic form,

n signifies an integer from 1 to 10 and

x signifies the corresponding valency of the proton (1) or metal cation (1,2,3 or 4), as the catalyst in an organic solvent.

2. A process according to claim 1, wherein an aliphatic or cyclic ketone, an aliphatic or cyclic ester, or an aliphatic or aromatic hydrocarbon, is used as the organic solvent.

3. A process according to claim 2, wherein the solvent is isobutyl methyl ketone, diethyl ketone, cyclopentanone, isophorone, ethyl acetate, isopropyl acetate, γ-butyrolactone, ethylene carbonate, propylene carbonate, hexane, heptane, octane, benzene, toluene or xylene.

4. A process according to any one of claims 1 to 3, wherein the amount of tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methane or a metal tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methide of the formula I used as the catalyst is from about 0.1 mole% to about 2 mole% based on the amount of trimethylhydroquinone or isophytol/phytol, which is in the lesser molar amount.

5. A process according to any one of claims 1 to 4, wherein in addition to a metal tris(perfluoroalkanesulphonyl or pentafluorobenzenesulphonyl)methide of the formula I a Bronsted acid is used as a co-catalyst, preferably sulphuric acid, phosphoric acid or p-toluenesulphonic acid.

6. A process according to any one of claims 1 to 5, wherein about 10 - 100 ml, preferably about 30 - 60 ml, of organic solvent are used per 10 mmol of isophytol or phytol, whichever is employed.

7. A process according to any one of claims 1 to 6, wherein the reaction is effected at temperatures between about 60°C and about 150°C, preferably between about 100°C and about 120°C.

8. A process according to any one of claims 1 to 7, wherein the molar ratio of trimethylhydroquinone to isophytol/phytol present in the reaction mixture extends from about 1.3 : 1 to about 2.5 : 1, preferably from about 1.5 : 1 to about 2.2 : 1, and is most preferably about 2 : 1.

9. A process according to any one of claims 1 to 8, wherein isophytol or phytol, as such or in solution, is added portionwise to a suspension or solution of the trimethylhydroquinone and the catalyst.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 10 5979

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,Y	WO 98 21197 A (F. HOFFMANN-LA ROCHE) 22 May 1998 (1998-05-22) * page 4, line 24 - page 7, line 25; claims; examples *	1-9	C07D311/72
D,Y	US 5 554 664 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 10 September 1996 (1996-09-10) * column 3, line 22 - column 4, line 41; claims; examples 1-3 *	1-9	
D,A	EP 0 658 552 A (EISAI CO.) 21 June 1995 (1995-06-21) * claims; examples *	1-9	
D,A	EP 0 949 255 A (F. HOFFMANN-LA ROCHE) 13 October 1999 (1999-10-13) * claims; examples *	1-9	
P,Y	EP 1 000 940 A (F. HOFFMANN-LA ROCHE) 17 May 2000 (2000-05-17) * claims; examples *	1-9	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	11 June 2001	Helps, I

CATEGORY OF CITED DOCUMENTS
X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 10 5979

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

11-06-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9821197 A	22-05-1998	CN 1237163 A	01-12-1999
		EP 0937055 A	25-08-1999
		US 5908939 A	01-06-1999
US 5554664 A	10-09-1996	AU 4776696 A	23-09-1996
		CA 2213465 A	12-09-1996
		CN 1177346 A	25-03-1998
		DE 69610294 D	19-10-2000
		DE 69610294 T	12-04-2001
		EP 0813521 A	29-12-1997
		JP 11501909 T	16-02-1999
		WO 9627584 A	12-09-1996
EP 658552 A	21-06-1995	JP 7224054 A	22-08-1995
		CA 2137481 A	15-06-1995
		CN 1108254 A,B	13-09-1995
		DE 69417527 D	06-05-1999
		DE 69417527 T	26-08-1999
		US 5532387 A	02-07-1996
EP 949255 A	13-10-1999	BR 9902217 A	02-05-2000
		CN 1234402 A	10-11-1999
		JP 2000053673 A	22-02-2000
		US 6066745 A	23-05-2000
EP 1000940 A	17-05-2000	BR 9905319 A	17-04-2001
		CN 1253950 A	24-05-2000
		JP 2000143656 A	26-05-2000

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82